REMARKS

I. Status of the Claims

Claims 1-16 were canceled in a Preliminary Amendment submitted September 04, 2003. Claims 17-25 were canceled in an Amendment and Response to Restriction Requirement submitted October 14, 2003. Claims 34-36 were amended and new claim 40 was added in an Amendment submitted February 18, 2004. Claims 26 and 30 were amended and new claim 41 was added in an Amendment submitted June 18, 2004.

Claims 26, 28, 35, 36, and 39 have been amended and claims 27 and 41 have been canceled in the Amendment submitted herewith. Claims 26 and 28-40 are therefore presently pending in the application.

II. Claim Objections

Claim 36 is objected to because of the non-conventional ordering of the booster dosage ranges. Applicants assert that the dosage range recited in claim 36 is a typographical error. Claim 36 has been amended in the Amendment submitted herewith, wherein the dosage range of "1×10^{10} to 8×10^{8}" has been deleted and the dosage range of "1×10^{10} to 8×10^{10}" inserted therefore. Support for this amendment can be found in original claim 12, which was canceled in the Preliminary Amendment submitted September 04, 2003. Applicants therefore respectfully request withdrawal of the objection of claim 36.

III. Claims Rejected Under 35 U.S.C. § 112, First Paragraph

Claims 36, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Action states that the rejection is a "new matter rejection", as the claims allegedly contain subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Action rejects claim 36 under 35 U.S.C. 112, first paragraph, alleging that the recitation of a booster dosage range of about 1×10^{10} to 8×10^{10} pfu of virus does not have support in the original disclosure. Applicants respectfully traverse this rejection. As set forth above in Section II, the booster dosage range of about "1×10^{10} to 8×10^{8}" pfu of virus was a typographical error and has been amended to recite "1×10^{10} to 8×10^{10}". Support for this amendment can be found in original claim 12. Applicants therefore assert that the recitation of the booster dosage range of about 1×10^{10} to 8×10^{10} pfu of virus complies with the written description requirement and as such, respectfully request withdrawal of the rejection of claim 36 under 35 U.S.C. 112, first paragraph.

The Action rejects claim 39 under 35 U.S.C. 112, first paragraph, alleging that the recitation of an adenovirus comprising "a deletion in the E3 gene and a deletion in the E1 gene or the E5 gene" does not have support in the specification. Applicants respectfully traverse this rejection. Applicants have amended claim 39 in the Amendment submitted herewith, wherein the term "E5 gene" has been deleted from the claim. Support for a deletion of the "E3 gene" and the "E1 gene" can be found at least at page 5, lines 4 through 6 of the specification. Applicants assert that at the time of the present invention, it was known to one of skill in the art that that the adenovirus E3 and E1 genes were expendable regions of the viral genome, and that one could delete either or both of these genes. For example, U.S. Patent 4,920,209, cited in the present Action, describes making E1, E3 and E1/E3 deletions in the adenovirus types 4, 5 and 7 genomes (column 3, line 31 through column 4, line 18). Applicants therefore contend that there is adequate support and written description in the specification for the recitation of "an adenovirus comprising a deletion in the E3 gene and a deletion in the E1 gene", and as such, respectfully request withdrawal of the rejection of claim 39 under 35 U.S.C. 112, first paragraph.

The Action rejects claim 41 under 35 U.S.C. 112, first paragraph, alleging that the recitation of an adenovirus comprising "a gp120 sequence from an HIV-1 MN strain or LAV strain" does not have support in the specification. Claim 41 has been canceled, and as

such, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

IV. Claims Rejected Under 35 U.S.C. § 103

Claims 26-41 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Hung *et al.* (*Nat Immun Cell Growth Regul*, 9(3):160-164, 1990) in view of Davis *et al.* (U.S. Patent 4,920,209). The Action alleges that Hung *et al.* teaches an immunogenic composition of the presently claimed invention (*i.e.*, claim 26) and that one of skill in the art would have been motivated at the time the invention was made to administer the composition to a human and "experiment" with the methodologies to arrive at a prime-boost regimen. The Action rejects dependent claims 27-41, alleging that it would have been obvious to one of skill in the art to: (a) administer booster env and/or gag protein subunits, (b) "experiment" with the subunit antigen dosage amounts, (c) insert the *rev* gene in frame and after the *env* gene but before the poly-A signal sequence and (d) select the appropriate HIV-1 strains. The Action further alleges that Davis *et al.* teaches the deletion of both the E1 and E3 regions which can be used in connection with the adenovirus having a deletion in the E3 region taught by Hung *et al.*

Claims 26-31 and 33-41 are further rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Chanda *et al.*, 1990 (*Int. Rev. Immunol.*, 7(1):67-77, 1990) in view of Davis *et al.* (U.S. Patent 4,920,209). The Action alleges that Chanda *et al.* teaches an immunogenic composition comprising a recombinant adenovirus construct of the present invention, suggests that the composition can be used as a live recombinant vaccine against infectivity, and that one of skill in the art at the time the invention was made would have been motivated to administer this vaccine to a human to induce an immune response against HIV-1 infection. The Action rejects dependent claims 27-31 and 33-41, alleging that it would have been obvious to one of skill in the art to: (a) "experiment" with various methodologies of administering the composition, such as prime-boost methods, (b) administer to the subject intramuscular injections of the env and/or gag polypeptide, (c) "experiment" with the antigen

dose amounts to determine the optimal dosage to optimize an immune response, (d) "experiment" with the location of the *rev* gene in relation to the *env* gene, (e) select the appropriate HIV-1 strains such as LAV and MN and (f) "experiment" with the dosage amount of virus for a specific group of subjects. The Action further alleges that Davis *et al.* teaches the deletion of both the E1 and E3 regions which can be used in connection with the adenovirus having a deletion in the E3 region taught by Chanda *et al.* Applicants respectfully traverse these rejections.

Independent claim 26 of the present invention, as amended herein, is directed to a method for producing an immune response against HIV-1 infection in a human comprising (1) administering an intranasal or an intramuscular dosage of a recombinant adenovirus comprising an expression cassette containing a promoter, a nucleic acid sequence encoding the HIV-1 gp160 or gp120 polypeptide sequence and a polyadenylation signal sequence and (2) administering one or more intranasal or intramuscular booster dosages of the recombinant adenovirus. Claims 28-40 are dependent from claim 26.

Applicants' data clearly demonstrate that the claimed adenovirus constructs are immunogenic in both dogs (Treatment Regimen 4, pages 24-25 and Treatment Regimen 5, pages 25-27) and non-human primates (*i.e.*, chimpanzees) (Treatment Regimens 1-3, pages 13-23 and Treatment Regimen 6, pages 27-32). Furthermore, Applicants' data was the first to demonstrate protection of non-human primates against HIV-1 challenge (Treatment Regimen 6).

The Hung *et al.* reference describes a recombinant adenovirus type 7 (Ad7) construct comprising a gene expressing either the hepatitis B surface antigen (HBsAg) or the human immunodeficiency virus type 1 envelope glycoprotein (*env*). Hung *et al.* demonstrate that the Ad7-HBsAg construct is propagated in cultured cells and that propagation of the Ad7-*env* construct in cultured cells required co-infection with an Ad7 construct expressing the HIV-1 *rev* gene. Hung *et al.* further demonstrated that intra-tracheal inoculation of dogs with the Ad7-HBsAg construct induced an antibody response. Similar studies in dogs were not performed with the Ad7-*env* construct. Thus, there is no *in vivo* data or description in the

Hung *et al.* reference to suggest that the Ad7-*env* would in fact elicit an immune response in dogs or any other mammals. Furthermore, Hung *et al.* does not teach or suggest administering one or more intranasal or intramuscular booster dosages of the recombinant adenovirus as presently claimed. Applicants therefore assert that Hung *et al.* does not teach nor describe the presently claimed prime-boost method for producing an immune response against HIV-1 infection in a human.

The Chanda *et al.* reference describes a recombinant Ad7 construct comprising the HIV-1 *env* gene (Ad7-*env*), the major late promoter (MLP), the tripartite leader (TPL) and a poly-A sequence. Chanda *et al.* also describe a second Ad7 construct comprising both the *env* and *rev* genes (Ad7-*rev-env*). Chanda *et al.* demonstrated that the env protein is expressed in A549 and HEK cells infected with Ad7-*env* or Ad7-*rev-env*. Chanda *et al.* immunized dogs with an Ad7 construct expressing hepatitis B surface antigen (HbsAg, *i.e.*, an Ad7-HbsAg construct) and observed an anti-HBs response, stating that "the data demonstrate that under semi-permissive conditions, adenovirus vectors may induce seroconversion to products of foreign gene inserts". Chanda *et al.* did not perform a similar study in dogs with the Ad7-*env* or Ad7-*env-rev* constructs. Thus, there is no *in vivo* data in the Chanda *et al.* reference to suggest that the Ad7-*env* would in fact elicit an immune response in dogs or any other mammals. Furthermore, Chanda *et al.* does not teach or suggest administering one or more intranasal or intramuscular booster dosages of the recombinant adenovirus as presently claimed. Applicants therefore assert that Chanda *et al.* does not teach nor describe the presently claimed adenovirus vectored prime-boost method for producing an immune response against HIV-1 infection in a human.

The allegation that one of skill in the art, at the time the invention was made, would have been motivated by the teachings of the Hung *et al.* or the Chanda *et al.* reference to (a) administer the presently claimed immunogenic composition to a human to induce an immune response against HIV-1 infection, (b) "experiment" with the methodologies to arrive at a prime-boost regimen, (c) administer booster env and/or gag protein subunits, (d) "experiment" with the subunit antigen dosage amounts, (e) insert the *rev* gene in frame and

after the *env* gene but before the poly-A signal sequence and (f) select the appropriate HIV-1 strains; and "that one of skill would have had a reasonable expectation of success for doing so because Hung *et al.* and Chanda *et al.* teach vaccines comprising recombinant adenovirus that expresses HIV-1" is simply not correct.

This invitation to "experiment" argument made by the Examiner is an "obvious-to-try" rejection, which is not the standard for obviousness under 35 U.S.C. § 103. "Obvious-to-try has long been held not to constitute obviousness". *In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).*

> An obvious-to-try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co., 902 F.2d 943, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).*

More specifically, as was stated in *In re Dow Chemical*, 5 USPQ2d 1529, 1532 (Fed.Cir. 1988), "obvious to experiment" is not an appropriate test of obviousness: "The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a teaching or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."

Given the state of the art at the time of the present invention, a person of skill in the art would not have been motivated by the Hung *et al.* reference or the Chanda *et al.* reference (which provide no *in vivo* data with regard to the Ad7-HIV-1 *env* immunogenicity) to administer this construct to a human to induce an immune response against HIV-1 infection. Furthermore, in the absence of Applicants' data set forth above, one of skill would not have had a reasonable expectation of success based on the disclosure of either the Hung *et al.* reference or the Chanda *et al.* reference. Applicants contend that neither Hung *et al.* nor Chanda *et al.*, taken alone or in combination with Davis *et al.*, render the presently

claimed invention obvious, and as such, respectfully request withdrawal of the rejection of claims 26-41 under 35 U.S.C. § 103.

V. Double Patenting Rejections

Claims 40 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent 6,511,845. Applicants respectfully traverse this rejection.

Applicants submitted, February 18, 2004, a terminal disclaimer to obviate the double patenting rejection of the present application (U.S. Application No. 09/457,421) over claims 1-24 of U.S. Patent 6,511,845. In the Office Action mailed March 19, 2004, the Examiner indicated that the terminal disclaimer had been approved by the "Office" and that the rejection had been withdrawn. Applicants therefore respectfully request withdrawal of the rejection of claims 40 and 41 are under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent 6,511,845.

Claims 26-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending U.S. Application No. 10/794,876. Applicants respectfully traverse this rejection.

The present application, U.S. Application No. 09/457,421, received a two-way Restriction Requirement in an Action mailed September 25, 2003. The Restriction Requirement split the claims into two groups: Group I, claims drawn to a composition comprising a recombinant adenovirus, classified in class 435, subclass 235.1 and Group II, claims drawn to a method for producing an immune response against HIV-1 infection, classified in class 424, subclass 233.1. In response to the Restriction Requirement, submitted October 14, 2003, Applicants elected to prosecute the invention according to Group II, claims directed to a method for producing an immune response against HIV-1 infection. On March 05, 2004, Applicants filed a divisional application, U.S. Application No. 10/794,876, wherein the claims set forth in the Preliminary Amendment were directed to the claims defined in the parent application as Group I (*i.e.*, claims directed to a composition comprising a recombinant adenovirus).

Applicants therefore assert that the provisional obviousness-type double patenting rejection of claims 26-41 of the present application, over claims 1-16 of copending U.S. Application No. 10/794,876, is not proper under 35 U.S.C. § 121, and as such respectfully request withdrawal of the rejection.

If there are any matters which may be resolved or clarified through a telephone interview, the Examiner is requested to contact the undersigned Agent at the number indicated.

The notice set a three-month period to comply, to and including December 22, 2004. Thus, this response is believed to be timely filed and no fees should be due. Should any fees be deemed necessary, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-1425.

Respectfully submitted,

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